REMARKS

Upon entry of the amendments herein, claims 1-20 and 24-37 remain pending in the application. Claim 1 has been amended herein. No new matter has been introduced thereby.

Applicants acknowledge with gratitude the time the Examiner took on January 11, 2007 to discuss some of the issues with the undersigned.

The Examiner has leveled a restriction requirement, dividing the claimed subject matter into 10 restriction groups, each allegedly being drawn to a patentably distinct invention. In response, Applicants hereby elect, with traverse, restriction group I, claims 1-11, 33 and 34, drawn to an isolated Nurr1 gene, or a functional fragment or variant thereof, which contains one or more mutations as specified, as well as vectors and host cells comprising the gene, fragment or variant.

The Examiner has correctly identified, at least in part, the special technical feature of the present invention. However, the Examiner asserts that the claims in their present state do not exclude variants of the mutant Nurr1 gene that are disclosed by Castillo et al. Thus, the Examiner concludes that the special technical feature of the present invention "does not make a contribution over the prior art" and, as a consequence, that unity of invention does not exist. The Examiner's assessment is in error.

It appears that the Examiner has not correctly interpreted the scope of instant claim 1; the Examiner appears to believe that the fragments and variants of the mutant Nurr1 gene do not necessarily have to contain the mutation(s) that are in the gene from which they are derived. However, as the Examiner recognizes, it is the particular mutations that are the basis for the present invention. The intent is clearly that all

nucleic acids falling within the scope of the claims must have one or more of the recited mutations. The Examiner's attention is called to, for example, the passage in the instant specification on page 5, lines 25-28. The teaching of the specification notwithstanding, Applicants have amended claim 1 to remove any possible argument as to the intended scope of the claims.

Accordingly, the Castillo reference cited by the Examiner provides no basis for assertion of lack of unity of invention. As the Examiner has acknowledged, the special technical feature of the present invention involves specific mutations in the Nurr1 gene and, as the Examiner further has acknowledged, Castillo does not recite those mutations. Thus, the restriction is improper and must be withdrawn; withdrawal is respectfully requested.

The Examiner has leveled a further restriction of each of the 10 main groups, requiring the election of a single mutation or a specific combination of mutations (in the January 2007 telephone discussion, the Examiner confirmed that it was not, as stated in the Action, a requirement to select a single gene or combination of genes). In response, Applicants hereby elect, with emphatic traverse, the mutation Met97Val.

In the written Action, the Examiner emphasizes that this is not an election of species, thus indicating that Applicants' election would not serve as the basis for initial examination with the prospect of expansion of the scope of examined subject matter. However, the Examiner did indicate during the January 11, 2007 telephone discussion with the undersigned that this part of the restriction would be reconsidered upon the providing of convincing arguments and/or evidence that any one of the specified mutations would have the same effect as any other one of the mutations.

As disclosed in the specification, all of the specifically recited mutations are found in exon 3 of the Nurr1 gene and, as disclosed throughout the specification, all of the mutations have in common that they show a link between the Nurr1 gene and neuropsychiatric disorders; in particular, the specified mutations are linked to schizophrenia and manic depressive illness but not, for example, to Parkinson's disease. Parkinson's is a nervous-system disorder connected with dopamine, but is not a neuropsychiatric disorder. That such a link exists is borne out by the observations that a) the three mutations were clustered in exon 3 within 78 basepairs of the N-terminal domain, b) the mutations all lead to impaired Nurr1 transcriptional activity and c) except for these mutations, there was total conservation of the gene sequence. The Examiner's attention is drawn to such exemplary specification passages as the one running from page 6, line 22 through page 7, line 9 and the one running from page 25, line 27 through page 26, line 2. The Examiner's attention is further drawn to the published paper of Buervenich et al., Am. J. Med. Genetics 96, 808-813 (2000), a copy of which is provided herewith. This publication and the present application are based on the same studies. The publication provides further details of, and support for, the inventive concept described in the present application and for which Applicants are entitled to receive a patent.

Even in the absence of the telling support provided by Applicants, the Examiner's stance with regard to this further restriction based on the mutations must be considered arbitrary and unwarranted. This is particularly so in view of the fact that the Examiner is not treating this aspect of the restriction as a standard election of species.

There is no basis or precedent in the case law for taking such a stance. The Examiner states that "[E]ach molecule of a mutant Nurr1 gene or protein is chemically and structurally distinct from another mutant, thus do not share the same special technical feature with one another." This assessment is certainly inappropriate.

Asserting in the present case that each of the specified mutants is chemically and structurally distinct from any other of the specified mutants is like asserting in a chemical case that each species encompassed by a generic formula is patentably distinct from all the others simply because each has some difference in the variable substituents. Clearly any difference in substituents would give rise to a species that literally is "structurally different." However, just as clearly, the understanding has been that members of a genus are alike chemically; this is the basis for allowing a genus of compounds in a single patent application. If the Examiner's were a proper application of U.S. practice, there would exist none of the multitude of chemical patents already issued that are directed to groups of compounds defined by generic formulae; every such issued patent would instead be directed only to a single compound. Clearly, this is not in the spirit of U.S. patent practice.

In any event, as clearly set forth above, the genes carrying the various recited mutations have properties in common, and these properties comprise a special technical feature that defines a contribution over the prior art. This aspect of the restriction must also be withdrawn; withdrawal is respectfully requested.

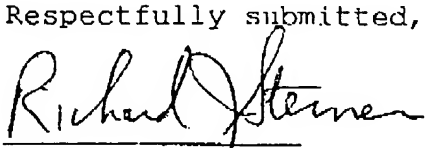
In light of the arguments set forth above and the amendment of claim 1 herein, no valid case can be made either for the division of the subject matter into the 10 basic restriction

groups or to the further restriction to a single mutation or combination of mutations. It is respectfully requested that this application now proceed to substantive examination and that all of the pending claims be examined together and in their present scope.

No additional fees should be due in connection with this communication. However, should it be determined that an additional fee is required for any reason, the Commissioner is hereby authorized to charge it to Deposit Account No. 23-1703.

Dated: February 14, 2007

Respectfully submitted,



Richard J. Sterner
Reg. No. 35,372

Customer No. 007470
(212) 819-8200

Agent's Direct Line:
(212) 819-8783

Enclosure

American Journal of Medical Genetics (Neuropsychiatric Genetics) 96:808–813 (2000)

Brief Research Communication

NURR1 Mutations in Cases of Schizophrenia and Manic-Depressive Disorder

Silvia Buervenich,[1,2] Andrea Carmine,[1,2] Mariette Arvidsson,[3] Fengqing Xiang,[2,4] Zhiping Zhang,[2,4] Olof Sydow,[5] Erik G. Jönsson,[6] Göran C. Sedvall,[6] Sherry Leonard,[7] Randal G. Ross,[7] Robert Freedman,[7] Kodavali V. Chowdari,[8] Vishwajit L. Nimgaonkar,[8,9] Thomas Perlmann,[3] Maria Anvret,[2,4] and Lars Olson[1]*

[1]*Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden*
[2]*Department of Clinical Genetics, Center for Molecular Medicine, Karolinska Hospital, Stockholm, Sweden*
[3]*Ludwig Institute for Cancer Research, Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden*
[4]*Department of Clinical Neuroscience, Neurology Section, Karolinska Institutet, Stockholm, Sweden*
[5]*Karolinska Institutet, Division of Neurology, Danderyd's Hospital, Danderyd, Sweden*
[6]*Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden*
[7]*Department of Psychiatry, University of Colorado Health Science Center, Denver, Colorado*
[8]*Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania*
[9]*Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania*

Transgenic mice lacking the nuclear orphan transcription factor Nur-related receptor 1 (Nurr1) fail to develop mesencephalic dopamine neurons. There is a highly homologous *NURR1* gene in humans (formerly known as *NOT*) which therefore constitutes a good candidate gene for neurologic and psychiatric disorders with an involvement of the dopamine neuron system, such as Parkinson's disease, schizophrenia, and manic-depression. By direct sequencing of genomic DNA, we found two different missense mutations in the third exon of *NURR1* in two schizophrenic patients and another missense mutation in the same exon in an individual with manic-depressive disorder. All three mutations caused a similar reduction of in vitro transcriptional activity of NURR1 dimers of about 30–40%. Neither of these amino acid changes, nor any sequence changes whatsoever, were found in patients with Parkinson's disease or control DNA material of normal populations. Am. J. Med.

Genet. (Neuropsychiatr. Genet.) 96:808–813, 2000.

KEY WORDS: complex diseases; nervous system; genetic variant; nuclear orphan receptor; NGFI-B family; Parkinson

INTRODUCTION

Schizophrenia, bipolar affective disorder, and Parkinson's disease have in common that epidemiological studies have pointed out a higher risk for an individual of being affected when affected relatives are present, but the mode of inheritance of susceptibility is complex and has not yet been elucidated. A further common observation in the three different diseases is etiologic and/or therapeutic involvement of dopaminergic neurotransmission. Thus, cells of the mesostriatal midbrain dopamine (DA) neuron system degenerate in Parkinson's disease [Hornykiewicz, 1998], while the mesolimbic DA axis is the target of several antipsychotic drugs [Creese et al., 1976; Gerner et al., 1976; Carlsson, 1988]. Recently, a number of studies have pointed out the importance of retinoids and retinoid-related genes for DA cells [McCaffery and Dräger, 1994; Zetterström et al., 1996, 1999;]. Midbrain DA neurons express receptors for retinoic acid-mediated transcription, and mice lacking the retinoid-related receptor Nurr1 fail to develop mesencephalic DA neurons [Zetterström et al., 1997; Castillo et al., 1998; Saucedo-Cardenas et al., 1998]. The immediate early gene *NURR1* (also called *NOT* in humans, classified as NR4A2 according to the most recent nomenclature [Nuclear Receptors Nomenclature Committee, 1999]) codes for a nuclear orphan receptor of the NGFI-B family of transcription factors [Mages et al., 1994; Castillo

Andrea Carmine and Mariette Arvidsson contributed equally to this work.

The current address of Zhiping Zhang and Maria Anvret is AstraZeneca R&D Södertälje, 15185 Södertälje, Sweden.

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*Correspondence to: Lars Olson, Department of Neuroscience, Karolinska Institutet, 17177 Stockholm, Sweden.
E-mail: Lars.Olson@neuro.ki.se

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et al., 1997; Saucedo-Cardenas et al., 1997; Hazel et al., 1988]. The major splice variant is a 598 amino acid protein with ligand binding, DNA binding, and N-terminal domains. Recently, alternatively spliced mRNA variants encoding N-terminal and C-terminal domains of variable length have been isolated [Ichinose et al., 1999; Ohkura et al., 1999; Torii et al., 1999].

While no activating ligand for NURR1 has been identified to date, it has been shown that NURR1 can be both constitutively active as a transcription factor and dimerize with RXR, a receptor involved in mediating retinoic-acid-induced transcription [Perlmann and Jansson, 1995]. Heterozygous Nurr1 knockout mice have reduced amounts of DA in their brains [Zetterström et al., 1997] and RXR mutant mice display impaired locomotion and dopamine signaling [Krezel et al., 1998]. An overlap of schizophrenia linkage loci with retinoid related gene loci, among those *NURR1* on human chromosome 2q22-23, has been pointed out [Goodman, 1998]. These studies together with other observations [Samad et al., 1997; Goodman, 1998] have made *NURR1* a suggestive candidate gene for diseases with an involvement of the dopamine neuron system, such as schizophrenia, manic-depressive illness, and Parkinson's disease.

We chose the candidate gene approach and direct sequencing of the *NURR1* gene from patient DNA in order to identify any possible mutations that might confer susceptibility for disease without necessarily being fully penetrant.

MATERIALS AND METHODS

Subjects

Our patient material was obtained after informed consent. It consisted of 135 Swedish schizophrenia patients, three Swedish manic-depressed patients, 70 Swedish Parkinson patients, and 136 Swedish controls from Stockholm; 20 American schizophrenia patients and 90 American controls from Denver; 140 American schizophrenia patients from Pittsburgh; and material, purchased from the Coriell Cell Repository (Camden, USA), derived from 26 manic-depressed patients.

Swedish schizophrenic patients and control subjects consisted of unrelated Caucasian individuals living in Stockholm. They were assessed by clinical and/or structural interviews [Spitzer et al., 1986], medical records, and parish register data for psychiatric diagnosis, family history of psychosis in first- or second-degree relatives, and geographical origin as previously described [Jönsson et al., 1993, 1997]. All patient and control interviews and diagnostic formulations (DSM-III-R) were conducted by one of the authors (E.J.), a psychiatrist trained in Sweden. Genealogical reports suggested no significant difference in the national ancestry of cases or controls. Swedish Parkinson's patients were diagnosed according to the "brain bank clinical diagnostic criteria" for idiopathic Parkinson disease [Daniel and Lees, 1993], except that three cases had more than one affected relative but were still included. The three manic-depressed patients from Sweden had originally been included in the material as one presumed control and two schizophrenic patients. At the time of the present study they turned out to fulfil the DSM-III-R criteria for bipolar affective disorder.

American schizophrenic patients from Denver fulfilled the DSM-III-R or DSM-IV diagnostic criteria. Because childhood onset is uncommon in schizophrenia, we analyzed the karyotype of one childhood-onset mutation carrier without finding any anomaly. Additionally, the mother of the child, who is a 50-year-old carrier of the same mutation, underwent thorough neurological examination by a specialist who was able to exclude the presence of another primary neurological disease that might present with schizophrenia symptoms in the offspring.

American schizophrenic patients from Pittsburgh included unrelated Caucasian inpatients and outpatients (DSM-IV criteria). Clinical data were gathered using semistructured interviews and hospital records and venous blood samples obtained as described previously [Nimgaonkar et al., 1996; Rao et al., 1998].

American bipolar affective disorder patients belonged to Coriell families number 811 (n = 3), 812 (n = 2), 823 (n = 5), 830 (n = 4), 834 (n = 1), 835 (n = 1), 884 (n = 5), 888 (n = 1), 893 (n = 2), and 1,075 (n = 2). In the association study of the intronic BseRI polymorphism, only the 10 index cases of these families were included.

DNA Sequencing

DNA was extracted from whole blood according to standard protocols. The genomic structure of the human *NURR1* gene was deduced from the homologous mouse *Nurr1* gene, and primers covering the second exon (noncoding), the second intron and the entire coding region (exons 3–8) were designed (Table I). The numbering of nucleotides and amino acids employed by us follows the initial publication of the human *NURR1 (NOT)* mRNA sequence [Mages et al., 1994]. The sequence of the second intron was determined by sequencing of fragment 0, and one additional forward primer was designed located in the second intron (see Table I, Fig. 1). Polymerase chain reaction (PCR) was carried out using Taq DNA polymerase (Sigma, St. Louis, MO). Thirty-five cycles were run at 94°C for 40 sec, 56°C for 45 sec, and 72°C for 1 min. After PCR, the samples underwent electrophoresis on 1% low-melting agarose gels and were visualized using UV-translumination after ethidium bromide staining. DNA was extracted from gel slices (PCR preps DNA purification kit, SDS) and DNA fragments were sequenced using either Thermo Sequenase radiolabeled terminator cycle sequencing kit (Amersham, Cleveland, OH) followed by 6% polyacrylamide gel electrophoresis (National Diagnostics, Manville, NJ) or DTCS kit (Beckman Coulter, Palo Alto, CA) followed by automated capillary gel electrophoresis (CEQ 2000 system, Beckman Coulter). Allele frequencies of the polymorphic site in intron 6 were determined by restriction enzyme analysis using BseRI (New England Biolabs, Beverly, MA).

TABLE I. Primers Used to Amplify PCR Fragments of NURR1

Fragment number	Description	Primer sequences
0	Part of the second (noncoding) exon, intron 1 (complete) and 2 bases of exon 3	F–GGAGATTGGACAGGCTGGAC R–TGCGCCTGAACACAAGGCAT
1	The forward primer is located in the second intron, immediately adjacent to the border to the third exon. This fragment contains the first 513 bases of exon 3	F–TTATCACCCTGTTTCATTTCC R–GAGACTGGCGTTTTCCTCT
2	Second half of exon 3. Both primers are located within coding sequence	F–TGCCGCACTCCGGGTCGGTTTACTACA R–GCCCTCACAGGTGCGCACGCCGTA
3	Rest of exon 3, complete intron 3 and major part of exon 4	F–CACGCGTCTCAGCTGCTCGACAC R–CTTCTTTGACCATCCCAACAGCCA
4	Exon 4, intron 4 and exon 5	F–CGCACAGTGCAAAAAAATGCAA R–CCTGGAATAGTCCAGGCTGG
5	Exon 5, intron 5 and exon 6	F–TGGTTCGCACAGACAGTTTA R–GCTAATCGAAGGACAAACAG
6	Exon 6, intron 6 and exon 7	F–TTCCAGGCGAACCCTGACTA R–ACCATAGCCAGGGCAGCAAT
7	Exon 7, intron 7 and exon 8 including 34 bases of 3′ untranslated region	F–TCCAACCCAGTGGAGGGTAA R–ATTCCAGTTCCTTTGAAGTGC

In Vitro Expression Assay

Human *NURR1* cDNA sequence was cloned into the expression vector pCMX [Umesono et al., 1991] and expression vectors for the mutants were generated by site-directed mutagenesis (GeneEditor In Vitro Site-Directed Mutagenesis System; Promega, Madison, WI). A double-stranded NurRE [Philips et al., 1997] DNA fragment was generated by annealing the primers 5′-AGC TTG TGA TAT TTA CCT CCA AAT GCC AG-3′ and 5′-AGC TCT GGC ATT TGG AGG TAA ATA TCA CA-3′. A luciferase reporter plasmid containing three tandem NurRE sites was generated by ligating the annealed fragments upstream of the herpes simplex thymidine kinase promoter fused to the luciferase gene. Human embryonic kidney (HEK)-293 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (FCS). Transfections were performed in 24-well plates by the calcium phosphate method. Briefly, cells were seeded 1 day prior to transfection. Cells in each well were treated with 100 ng of the indicated expression vectors, 100 ng of reporter plasmid, and 200 ng of reference CMX-βgal plasmid containing the β-galactosidase gene and CMX-PL1 as carrier DNA up to 500 ng of total DNA. Cells were exposed to calcium phosphate precipitate for 12–16 h and washed with PBS and then fresh medium was added. The cells were harvested and lysed after 36 h incubation. Extracts were assayed for luciferase and β-galactosidase activity in a microplate luminometer/photometer reader (Lucy-1, Anthos). All luciferase activities were normalized to β-galactosidase activity.

RESULTS

In the first stage of this study we sequenced the entire coding region of the *NURR1* gene [Mages et al., 1994] in 20 patients with Parkinson's disease, 20 patients with schizophrenia, and four healthy control individuals, all Caucasians. We identified one deletion of three basepairs (ΔY122, Figs. 1, 2) in one childhood-onset schizophrenic individual originating from the USA. This mutation was located in PCR fragment 1, which covers about the first half of the N-terminal domain (Fig. 1).

Disease-causing mutations are frequently clustered in coding regions of the corresponding genes. Therefore, we continued our sequencing efforts by focusing

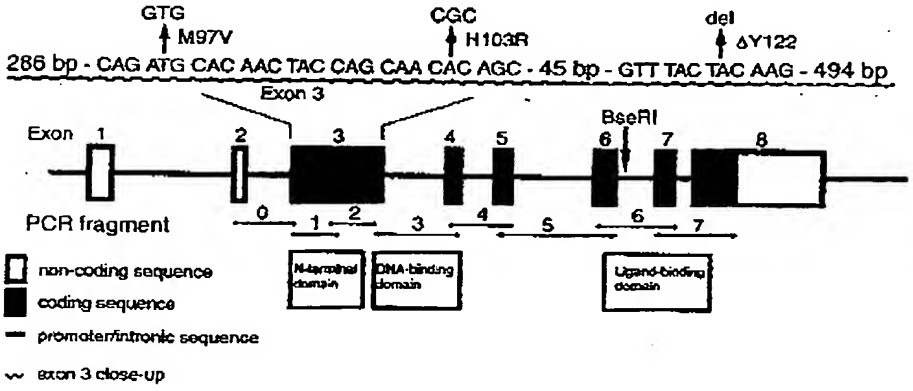

Fig. 1. Overview of genomic structure of the human *NURR1* gene, distribution of PCR fragments 0–7, localization of the three mutations in exon 3, and position of the BseRI polymorphism in intron 6. All three mutations are localized within 78 basepairs of PCR fragment 1, comprising the first 495 bases of exon 3. Fragment 0 was only sequenced once in order to design a new primer within the second intron closely adjacent to exon 3.

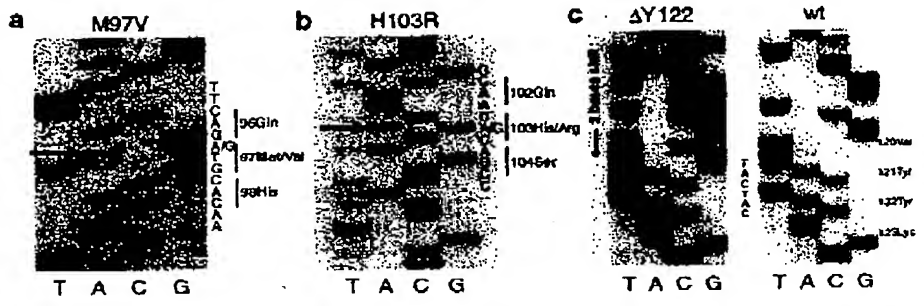

Fig. 2. Autoradiographs of the three heterozygous mutations. a: M97V leads to a double band at the first nucleotide of the codon for amino acid position 97. The arrow points to the wild-type band. b: H103R exchanges the middle nucleotide in the codon for amino acid 103. The arrow indicates the wild-type. c: ΔY122 deletes one of the tyrosines at positions 121 or 122. It is not possible to tell which three consecutive bands have been deleted. However, the pattern of the three basepair shift beginning at the TACTAC sequence must result from a three basepair deletion within these six basepairs and the surrounding amino acid sequence is not affected by this shift. Because a reverse primer was used for generating this autoradiograph, the shift occurs in the adjacent sequence above the double tyrosine codons. On the right, the wild-type (wt) sequence is shown for comparison.

on PCR fragment 1. We sequenced this fragment in 132 Swedish controls, 90 American controls, 50 additional Swedish Parkinson patients, 135 additional Swedish schizophrenic patients, and 29 manic-depressed patients from the USA and Sweden. We identified one missense mutation (H103R; Figs. 1, 2) in a Swedish schizophrenic patient and another missense mutation (M97V; Figs. 1, 2) in a Swedish patient with manic-depressive illness with psychotic symptoms. All three mutations were absent from all other DNA samples. It is therefore unlikely that these sequence changes are polymorphic variants (i.e., have an allele frequency of more than 1% in the normal population) of the human *NURR1* gene. We did not find any synonymous or non-synonymous polymorphism in the sequenced coding region of *NURR1*, a gene with a very high degree of conservation at the protein level between human, mouse, and rat sequences (99.5% and 97.6% identity, respectively). However, we did identify one common polymorphic site in the sixth intron, 18 bases downstream of the border to the sixth exon, deleting a BseRI cleavage site by a single base insertion. The allele frequency of the less common allele was found to be 15.4–30.0% in different samples of our patient groups studied (Table II). We used this polymorphism in order to determine genetic diversity at the *NURR1* locus in our material. Allele frequencies in American and Swedish controls of Caucasian origin were found to be virtually identical, consistent with a similar genetic background of these two populations. The differences of frequencies in the patient groups as compared to controls were not significant.

TABLE II. Distribution of Intron 6 BseRI Polymorphism in Patient and Control Samples

Sample	Intron 6 BseRI polymorphism frequency	n (Chromosomes)
Swedish controls	21.8%	142
American controls	22.0%	124
Swedish SZ	23.1%	134
American SZ	30.0%	40
American MD	25.0%	20*
Swedish PD	15.4%	104

*Index cases of Coriell families.
SZ: schizophrenia; MD: manic-depression; PD: Parkinson's disease.

The fact that we detected three very rare missense variants of the *NURR1* gene in close vicinity to each other in the third exon in patient material exclusively suggested a role of the identified mutations in the pathogenesis of schizophrenia and manic-depression. To further evaluate the possible significance of the clustered mutations identified in our material, we therefore analyzed a further, independent material of 140 samples taken from schizophrenic subjects of American Caucasian origin. However, in this sample neither the three mutations described above nor any other mutations or polymorphisms were identified in the entire third exon of *NURR1*.

Because the rarity of molecular variants of *NURR1* does not exclude their role in the pathogenesis of psychiatric disease in those individuals where they were identified, we also set up functional assays in order to elucidate if any of the three clustered mutations might affect *NURR1* function.

NURR1 transcriptional activity was measured using human embryonic kidney (HEK)-293 cells monitoring NURR1 homodimer binding to NurRE [Philips et al., 1997]. Each experiment was carried out using two independent clones for the wild-type and mutated vectors, respectively, and activity was measured in at least four separate wells for each clone. We found a significant reduction (30–40%) of transcriptional activity of mutated NURR1 homodimers. This reduction was strikingly similar in all three mutated clones and is consistent with our finding that the three mutations are clustered in a region of NURR1 which is critically important for transcriptional activation. Figure 3 shows results of one representative experiment. The average activity and SEM of mutated NURR1 in percent of wild-type activity in all experiments carried out were ΔY122: 0.645 ± 0.024, n = 87; H103R: 0.608 ± 0.036, n = 87; and M97V: 0.661 ± 0.046, n = 54.

Attempts to obtain DNA samples from relatives of the three mutation carriers for further genetic studies were only moderately successful. Only in the childhood-onset case (carrier of ΔY122) was it possible to obtain parental DNA. The mother was a healthy car-

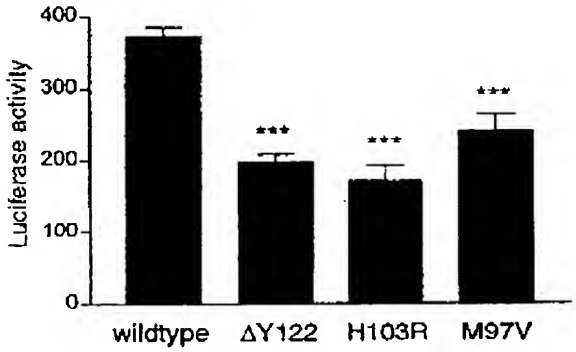

Fig. 3. Graphical illustration of a representative transfection experiment. Each column represents the means of 12 independent transfections of two individual clones for the wild-type and for each mutated vector. Error bars display standard errors of the mean. Student's *t*-test was carried out for all comparisons and two-tailed *P* values were determined. ***$P < 0.001$.

rier of the mutation, but no further family history could be obtained in this kindred. The medical and family histories of all three patients are summarized in Table III.

DISCUSSION

In total, two out of 295 patients with schizophrenia and one out of 29 patients with bipolar affective disorder carried unique but similarly effective mutations clustered in a small area of the N-terminal domain of the *NURR1* gene, while no polymorphisms or mutations were identified in the ethnically matched 226 controls or the 70 Parkinson patients included in this study. Therefore, the frequency of mutated *NURR1* determined by us is low (less than 1% for schizophrenia and 3% for bipolar disorder, the latter being a very rough estimate because of a small sample size and partial relationships between probands). However, the multifactorial etiology of schizophrenia and manic-depression is consistent with a limited occurrence of each individual genetic mutation, such as the ones described here. Multiple and diverse genetic mutations that predispose for disease may, however, have effects that converge to generate symptoms via a limited number of neuronal systems, including those that express *NURR1*, such as the dopamine system. The well-established role of Nurr1 for the development and function of mesencephalic dopamine neurons suggests that the disease-specific missense mutations found by us and demonstrated by site-directed mutagenesis to lead

TABLE III. Clinical Descriptions of the Three Heterozygous Mutation Carriers

Mutation	Diagnosis	Country of origin	Age of onset	Brief history	Family history
M97V	Schizophrenia	Sweden	26	Onset with auditory hallucinations, displayed later delusions of reference, paranoid delusions, verbal auditory hallucinosis, visual and tactile hallucinosis, thought insertion and thought 'broadcast', as well as flat and sometimes inappropriate affects. Responded well to antipsychotic treatment. Relapses after discontinuation of the antipsychotic medication. Currently on continous antipsychotic medication and has been free from psychotic episodes for several years.	The paternal grandmother's sister had been treated at a mental hospital, the cause of illness unknown.
H103R	Bipolar disorder with psychotic features	Sweden	21	First hospital admission after 5 months of expansive and irritable mood, decreased need for sleep, distractibility, and excessive involvement in pleasurable activities. In the end of this period also psychotic symptoms: verbal mood-congruent auditory hallucinations, delusions of reference, grandiose delusions, incoherence, and disorganized behaviour. Treatment with antipsychotic medication and discharge to an outpatient department. Rehospitalization a month later due to depressed mood, weight gain, loss of energy, feeling of worthlessness, difficulties to concentrate, and recurrent thought of death. No psychotic symptoms during later manic and depressive episodes. Currently treated with lithium for more than four years without relapses.	The patient reported no major psychiatric disturbances in the family history. However, the paternal grandfather was said to be a confidence trickster.
ΔY122	MD (past); Childhood-onset schizophrenia, SAD, ADHD (current)	USA	11	Two episodes of extended depressed mood and anhedonia (ages 6–7 and 10–11). Auditory hallucinations since the second episode. Hallucinations and delusions occur regularly and are independent of mood state. Intermittent history of obsessions and compulsions since age of 6. Frequent episodes of illogical thinking and neologisms and short periods of incoherent speech.	The mother reported a few occasional (olfactory, visual) hallucinatory episodes but no further symptoms.

MD: major depression; SAD: separation anxiety disorder; ADHD: attention deficit/hyperactivity disorder.

to impairments of NURR1 function may represent one such causative event pathway, increasing the risk of developing schizophrenia and/or bipolar disease. The observation that the *NURR1* gene may be a susceptibility locus for both diseases provides further evidence that common underlying genetic mechanisms may exist, as reflected in the literature by a large number of linkage studies pointing to overlapping genetic loci [for review, see Berrettini, 2000].

Because the *NURR1* gene is evolutionarily highly conserved and all amino acids affected by the mutations are identical in human and mice, generation of transgenic mice carrying the mutations should provide additional opportunities to understand how NURR1 function is affected. The generation of mice replicating the specific mutations found by us may help elucidate one pathway for the development of schizophrenia and/or bipolar affective disorder and thus may also help to find further genetic and environmental etiologic factors for these diseases.

While a larger patient material sample is needed to validate our findings, the fact that 1) the three mutations were clustered within 78 basepairs of the N-terminal domain, 2) they all lead to impaired NURR1 transcriptional activity in an in vitro bioassay, and 3) except for the three mutations this region of the *NURR1* gene was totally conserved at the DNA level in our entire material of 620 individuals (1,240 alleles) suggest that the *NURR1* gene does constitute an interesting candidate gene for mutations in diseases with an involvement of the dopamine system. Further studies of other regions of this gene, including the promoter, are warranted.

ACKNOWLEDGMENTS

We thank Hans-Werner Mages for providing the *NOT* (human *NURR1*) cDNA and Ann-Christin Thelander and Karin Lundströmer for technical assistance.

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